REMARKS

Claims 38-45 are pending in the application. Applicants are amending herewith Claim 39. Support for this amendment can be found generally throughout the specification and claims and specifically at page 21. No new matter is being introduced by this amendment. Therefore, applicants request entry of this amendment. Following entry of this amendment, Claims 38-45 are still pending in this application. Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following remarks.

The Office Action

The previous rejection of the claim under 35 U.S.C. § 102(b) as being anticipated by Ross et al. and under 35 U.S.C. § 102(b) as being anticipated by the patent to Smith et al. (U.S. Patent No. 6,310,072) alone was withdrawn.

Claim 39 was rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Claims 38-45 were rejected under 35 U.S.C. § 103 as being obvious over the article by Mercer, "Anesthesia for the Patient with Respiratory Disease (Practical Procedures 2000)" in view of the patent to Smith et al. (U.S. Patent No. 6,310,072).

The Rejection Under 35 U.S.C. §112

Claim 39 was rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The rejection states that the specification discloses the "ratio of about 1 to 0.66 by weight of [sic.; "to"] about 1 to 2.0 by weight," but does not provide support for the claimed ratio of 1:0.66 to 1:2.0 by weight. Applicants disagree. Applicants submit that the disclosure at Paragraph 0075, does indeed support the present claim language. There does not need to be word-for-word identity for the specification to provide support for a claim term. However, in order to advance prosecution, applicants are amending Claim 39 herewith to include the ration language that the Office Action acknowledges is support in the

specification. Applicants submit that this amendment does not narrow the scope of Claim 39. In view of the foregoing amendment, applicants respectfully request withdrawal of the rejection of Claim 39 under 35. U.S.C. §112.

The Rejection Under 35 U.S.C. §103

Claims 38-45 were rejected under 35 U.S.C. § 103 as being obvious over the article by Mercer in view of the patent to Smith et al. The rejection states that Mercer discloses that treating a patient with underlying respiratory disease is at increased risk of postoperative pulmonary complications with opioid analgesics and that pain relief, effective analgesia, reduces the incidence of post operative respiratory complications, but that respiratory depression is observed for and prevented. The rejection states that Mercer discloses that low doses of opioids in an epidural infusion results in the best analgesia with the fewest side effects. The rejection also states that Smith et al. discloses the same sub-analgesic amounts as presently claimed, and, thus Smith et al. intrinsically produces a reduced level of respiratory depression. The rejection concludes that it would have been obvious to the person of ordinary skill in the art at the time of the present invention to have used the method of producing analgesia, as taught by Smith et al., in the method of Mercer. Applicants respectfully disagree.

Mercer discloses:

> Intravenous opioid boluses can be titrated against pain in the recovery room, whilst observing for respiratory depression. This can be used as a guide to the dose on intramuscular opioid that may be given in relative safety on the ward. Continuous infusion of intravenous opioids demand very close supervision, as the risk of respiratory depression is significant.
> ***
> The combination of low concentrations of local anaesthetic with low doses of opioids in an epidural infusion results in the best analgesia for the fewest side effects (i.e. opioid induced respiratory depression and local anaesthetic toxicity). For example give 50 ml of 0.16% bupivacaine containing 5 mg diamorphine given as an epidural infusion at a rate of 0-8 ml/hr.

> While postoperative opioid analgesia is administered the patient must be observed in an area with sufficient medical and nursing skills, and staffing levels. Complications that may arise are then noted promptly and the appropriate help called. Regular observations are made of blood pressure, pulse, oxygenation (using pulse oximeter), respiratory rate, conscious level and analgesia. Protocols may be used to guide nursing staff in the administration of analgesia, the observations required and when to call for help.

Thus, Mercer disclose administering an analgesic dose of diamorphine in combination with a local anesthetic. Mercer appreciates the risks associated with morphine-induced respiratory depression, and, therefore, recommends observation and monitoring by competent staff. Mercer does not disclose that his treatment "produces an analgesic effect in the human and the human experiences a reduced level of respiratory depression than associated with a dosage of morphine or oxycodone required to achieve the same analgesic effect." This must be true because Mercer is administering an analgesic dose of morphine as a single opioid agent. Thus, Mercer does not discloses either a sub-analgesic dose or a combination of morphine and oxycodone. Furthermore, Mercer does not prevent respiratory depression. In fact, Mercer take great steps to observed for this condition because as he notes "the risk of respiratory depression is significant." Mercer utilizes trained nursing staff and close monitoring of vital signs and if a patient is in distress, "help" is called. Thus, Mercer reflects nothing more than the conventional use of analgesic amounts of a single opioid and careful monitoring for dangerous levels of respiratory depression.

Smith et al. does disclose administering a sub-analgesic dose of morphine in combination with a sub-analgesic dose of oxycodone to achieve the unexpected, synergistic result of analgesia in a human. Although Smith et al. discloses that some undesirable side-effects of the analgesia are reduced compared to analgesic doses, it does not disclose that this treatment reduced respiratory depression in humans. Smith et al. does disclose as follows:

> Close examination of the isobologram (FIG. 15) reveals that the optimum dosing combination comprised a 12-fold reduction in the morphine dose and a 4-fold reduction in the oxycodone dose compared with the s.c. doses of morphine plus oxycodone that would have been required to produce similar levels of antinociception had only additive antinociception occurred. Importantly, the marked antinociceptive synergy observed in our studies following s.c. co-administration of subanalgesic doses of morphine plus oxycodone was not due to motor deficits as rats did not lose their righting or landing reflexes even when the highest combined s.c. doses were administered. When this finding is combined with the additional observation that the incidence of sedation was reduced in these rats compared with rats receiving equipotent single s.c. doses of either morphine or oxycodone, our results indicate that it may be possible to achieve profound analgesia in humans with a reduced incidence of undesirable opioid side-effects (sedation, respiratory depression) by co-administering appropriate subanalgesic doses of morphine plus oxycodone.

Smith et al. at col. 24, lines 35-54. This statement is no more than speculation and conjecture and is not based on a reasonable expectation of success.

Simply put, Smith et al. fails to establish a reduced risk of respiratory depression associated with the administration of opioid analgesics when an analgesic effect is produced by administering a combination of a sub-analgesic dosage of morphine and a sub-analgesic dosage of oxycodone. For example, in Example 1 at col. 13, lines 7-12, it is commented that *"Following administration of the synergistic combination of morphine plus oxycodone, neither group of rats...displayed any adverse behavioural effects, such as sedation, incontinence and catatonia, one or more of which have been reported following large doses of either opioid alone."* In the Example 1 experiment, there was no control group dosed with an analgesic quantity of either oxycodone or morphine alone. Therefore, it is not possible to determine whether the side effects caused by an analgesic combination of oxycodone and morphine would be less than those caused by an analgesic quantity of either drug alone. From the passage quoted from above, it appears that "large doses" of opioid may be required to precipitate the side effects

of sedation, incontinence and catatonia in rats. Respiratory depression is conspicuously not mentioned as a side effect of such "large doses" of opioid.

Later at col. 13, lines 51-55, it is stated that *"Rats dosed with the synergistic combination of the two strong opioids, oxycodone and morphine, by both i.p. and i.c.v. routes displayed no observable adverse behavioural effects, such as catatonia, respiratory depression or marked sedation."* Although it is commented that the rats receiving the drug combination did not appear to display respiratory depression, there is no suggestion that they would have been at risk of doing so had they received an analgesic dose of either drug alone.

In conclusion, Example 1 fails to teach that respiratory depression is a side effect in rats treated with an analgesic dose of oxycodone or morphine alone, and therefore there is no suggestion that the alleged lack of respiratory depression in rats dosed with the combination of the two drugs reflects a risk of respiratory depression, respiratory cessation or sleep apnea associated with the administration of opioid analgesics that is reduced, as required by Claim 1.

Example 4 also refers to the side effects of opioids in rats. In the Example 4 experiment, "Cohort One" rats received a single dose of either morphine or oxycodone. "Cohort Two" rats received a combination of morphine and oxycodone. Col. 23, lines 45-51 state that *"In contrast to rats in Cohort One, some rats in Cohort Two that received combination doses of morphine plus oxycodone such that a maximal degree of antinociception was observed were behaviourally indistinguishable from control rats that received s.c. injections of normal saline, in that there were no apparent signs of sedation, respiratory depression or any other adverse opioid side-effects."* This passage, like the passages quoted from Example 1, fails to suggest that rats receiving a single dose of morphine or oxycodone had respiratory depression, only that they were not "behaviorally indistinguishable" from the mock-injected control rats, which would be the case if they exhibited <u>any</u> side effect of opioid administration. Thus, the fact that at least

some of the rats treated with the morphine plus oxycodone combination were behaviourally indistinguishable from the control rats and hence did not display respiratory depression, is not an indication that they had a reduced risk of respiratory depression, as compared to the Cohort one rats.

In fact, there appears to be no disclosure of a rat suffering from respiratory depression in Smith et al. Respiratory depression may be detected as reduced frequency and/or reduced amplitude of respiration. One would not necessarily expect to detect it merely by observational means, unless it was so extreme as to amount to respiratory cessation, and death. Yet, there is no indication in Smith et al. that suitable means were employed to identify respiratory depression. Therefore, there might have been a degree of respiratory depression in rats treated with the combination of opioids, without this having been detected.

The only side effect studied in Example 4 appears to be sedation as manifested by failure of an eye reflex test. Yet, there is no reason to suspect that a reduced risk of failing this test would be linked to reduced risk of respiratory depression.

Thus, the teaching of Smith et al. may be summarized as follows:

1. There is no disclosure of a rat suffering from respiratory depression in any group. As one would not necessarily be able to detect respiratory depression by observational means, the lack of observable respiratory depression in the groups of rats treated with sub-analgesic doses of morphine and oxycodone is inconclusive. This is because, if one wishes to rely on a "negative" result being truly negative, a positive control is required.

2. As there is no evidence that rats treated with an analgesic dose of morphine or oxycodone exhibited respiratory depression, there is no basis for comparison of the risk of respiratory depression between groups.

Assuming arguendo that the rats treated in Smith et al. did experience reduced respiratory depression, there is no basis for extrapolating those results to humans. Attached hereto, is a copy of an article by BG Oertel, et al. entitled "*The Partial 5-Hydroxytryptamine$_{1A}$ Receptor Agonist Buspirone does not Antagonize Morphine-induced Respiratory Depression in Humans*" (January 2007)(Exhibit 1), which states:

> Opioid analgesics are effective in the treatment of patients with severe pain. However, even under controlled clinical conditions opioid administration can result in fatal respiratory depression. [Citations omitted]. Therefore, selective antagonism of the respiratory depressive effects of opioids without decreasing their analgesic effects is clinically highly desirable. Pharmacological interactions involving various subtypes of serotonergic receptors in the central nervous system have been repeatedly proposed as a possible tool to counteract opioid-induced respiratory depression. For example, agonism at 5HT$_{4A}$ receptors has been demonstrated in rats to achieve this goal, but the presently only available 5HT$_{4A}$ agonist mosapride failed to achieve this goal in humans.

Oertel et al. at p. 59. Thus, in the case of mosapride, it reduced opioid-induced respiratory depression in rats, but was ineffective at reducing respiratory depression in humans.

Oertel et al. further states:

> Another approach to counteracting opioid induced respiratory depression involving serotonergic receptors is activation of 5-hydroxytryptamine (5-HT)$_{1A}$ receptors. Administration of the partial 5-HT$_{1A}$ receptor agonist 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) or buspirone restored normal respiratory function in rats with morphine-induced apnea.

Id.

Although Oertel et al. noted that the use of buspirone had been show to reduce morphine antinociception in animal models (*Id.* at p. 60), the test results that are the subject of this article failed to reduce the morphine-induced respiratory depression in humans (*Id.* at 65). Thus, in the case of respiratory depression, including sleep apnea, the results achieved with two different

drugs that in rodent studies antagonized the respiratory depression of morphine were ineffective at producing the same results in humans.

Oertel et al. is therefore significant for at least two reasons. First, it shows a long-felt but fulfilled need in the art for a way to reduce morphine-induced respiratory depression in humans. Although this article is not prior art *per se*, it is highly indicative of the state of the art at the time of the invention, since the article was received June 23, 2006 and accepted October 3, 2006. Thus, at the time of the present invention there was clearly a need to reduce morphine-induced respiratory depression in humans. However, as Oertel et al. clearly demonstrates, there was no known solution for this problem, at least not in humans. Second, Oertel et al. demonstrates that results in rats can not be extrapolated to humans predictably.

In view of the foregoing, it is submitted that Claims 38-45 are not obvious in view of the combination of Mercer and Smith et al. In a related application; *i.e.*, application serial No. 11/544,187, the claims were rejected as obvious based on a combination of Smith et al. and Riley et al. Applicants submit that the present claims are not obvious of the combination of Smith et al. and Riley et al. either.

With respect to Riley et al., the rejection in the related application improperly interprets the teaching of this article. The Office Action in the related application states that Riley et al discloses the use of 1-5 mg of morphine intravenously every 1 to 3 hours and the use of oral oxycodone to provide analgesia in patients with apnea. This is not correct.

Item #6 on page 649 of Riley et al. states:

> Analgesia consists of intravenous morphine sulfate or meperidine HCl in the ICU. Intravenous narcotics are administered by a nurse in graduated doses (e.g., morphine sulfate, 1 to 5 mg every 1 to 3 hours as needed) while monitoring respiratory rate. All nurses caring for patients with OSAS have been educated regarding the mechanism of sleep apnea and the use of narcotics. Patient-controlled analgesia is not used. Intramuscular meperidine HCl

> and oxycodone elixir are used in the surgical ward. Oral hydrocodone is used after discharge.

Riley et al. at 649.

Thus, Riley et al. discloses three separate stages of treatment. The first stage is in ICU where 1 to 5 mg of morphine alone is administered intravenously in graduating doses. Thus, although the dose of morphine may start out at a sub-analgesic dose, it is raised to a potentially analgesic dose of 5 mg. Furthermore, this is done only with careful monitoring of respiration by specially trained nursing staff. Second, in the surgery ward, intramuscular meperidine HCl and oxycodone elixir are used, but no specific amounts were stated by Riley et al. Additionally, it is not clear from this article that the meperidine HCl and oxycodone elixir are administered together. Finally, only after the patient is discharged is he or she given oral hydrocodone alone, but again, no amounts are provided. It is probably safe to assume that the amount of oral hydrocodone administered is an analgesic amount since the purpose of administering the single agent is to induce analgesia. Thus, contrary to the statement in the Office Action, Riley et al. does not disclose the co-administration of sub-analgesic amounts of morphine and sub-analgesic amounts of oxycodone.

In view of the unpredictability of extrapolating results in rats to humans and the specific failure of others to be able to duplicate the animal results of reduced morphine-induced respiratory depression in humans, the speculation in Smith et al. that "it may be possible to achieve profound analgesia in humans with a reduced incidence of undesirable opioid side-effects (sedation, respiratory depression) by co-administering appropriate subanalgesic doses of morphine plus oxycodone" (emphasis added) is mere speculation and does not provide a reasonable expectation of success. Combining the teaching of Riley et al. with Smith et al. does not produce the claimed invention. Contrary to the statement in the Office Action, Riley et al

does not disclose co-administration of morphine sulfate and oral oxycodone. Furthermore, there is no express disclosure in Riley et al. of the amount of oral oxycodone administered. In fact, it is submitted that the proper interpretation of Riley et al. is that the amount of oral oxycodone administered is an analgesic amount, which is a contrary teaching to the present invention. When the long-felt but unsatisfied need of finding a way to reduce the morphine-induced respiratory depression, as disclosed in Oertel et al., is considered, the present invention is clearly patentable over the prior art.

Furthermore, there was a strong technical prejudice against treating patients with respiratory illness with opioid analgesics. As evidence of this, enclosed is a package insert for Opana™ (oxymorphone hydrochloride) (Exhibit 2) which, as indicated at page 9 paragraph [0027] of the specification is a μ-opioid agonist.

The Opana™ package insert contains the following warning on page 7:

> RESPIRATORY DEPRESSION
> Respiratory depression is the chief hazard of OPANA. Respiratory depression is a particular potential problem in elderly or debilitated patients as well as in those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may dangerously decrease pulmonary ventilation.
>
> OPANA should be administered with extreme caution to patients with conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve such as: asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, CNS depression or coma. In these patients, even usual therapeutic doses of oxymorphone may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea. Alternative non-opioid analgesics should be considered, and oxymorphone should be employed only under careful medical supervision at the lowest effective dose in such patients"(emphasis added).

Also enclose is an excerpt from the WHO essential medicines library (Exhibit 3), which indicates that use of the μ-opioid agonist morphine is contraindicated in cases of acute respiratory depression (see page 2).

Also enclosed is Brodsky, Anesthesia for Bariatric Surgery (Exhibit 4), which states on page 5 in the section entitled "opioids" that *"Generous use of long-acting opioid analgesics (morphine, Demerol, hydromorphone) is dangerous since respiratory depression must be avoided."*

Also enclose is the abstract of Teichtahl *et al* (2001) *Addiction* 96: 395-403 (Exhibit 5), which identifies a higher prevalence of central sleep apnea in methadone maintenance patients (MMP) than in normal subjects, and suggests that this sleep disordered breathing might be related to sudden death.

There is thus a prejudice in the art that μ-opioid agonists should not be given to patients with respiratory illness, or should be given only with extreme caution. In addition, there was a strong technical prejudice against co-administering or concurrently administering combinations of opioid analgesics. The Opana™ package insert warns on page 9 that patients receiving other opioid analgesics with oxymorphone may exhibit an additive CNS depression. In particular, it is warned that interactive effects resulting in respiratory depression may occur.

Also enclose is an excerpt from "Cancer Pain Relief" (WHO, 1996) (Exhibit 6), which illustrates the sequential use of progressively strong pain relief on page 15. In group 3, an opioid for moderate to severe pain may be administered with or without a non-opioid analgesic and/or adjuvant drug. This option is recommended when an opioid for mild to moderate pain in combination with a non-opioid fails to relieve the pain, and it is stated that the opioid for moderate to severe pain should be substituted. Therefore, concurrent use of opioids in groups 2 and 3 is not recommended. Indeed, the recommendation is that *"only one drug from each of the*

groups should be used at the same time". In other words, if one opioid is used, it should not be used in combination with another opioid.

In view of the foregoing, it is submitted that Claims 38-45-11 are not obvious and unpatentable under 35 U.S.C. §103(a) over Mercer in view of Smith et al. or Smith et al. in view of Riley et al., and, therefore, withdrawal of the present rejection is respectfully requested.

Request for Telephone Interview

Applicants respectfully request an in office interview with the examiner. When this case reaches the examiner for action, applicants request that the examiner call the undersigned counsel to schedule the interview.

Conclusion

Applicants believe that the foregoing is a full and complete response to the Office Action. It is submitted that Claims 5-11 are now in condition for allowance. Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and remarks. Such action is courteously solicited. Applicants further request that the Examiner call the undersigned counsel at 404-572-2589 if allowance of the claims can be facilitated by examiner's amendment, telephone interview or otherwise.

Respectfully submitted,

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